REMARKS

In the Office Action dated October 3, 2008, claims 1-8 and 10-16 are pending and under examination. The Examiner has rejected claims 1-8, 10 and 12-16 under 35 U.S.C. §103(a) as allegedly obvious over Bochan et al. (*Transplant Proc* 31:690-91, 1999) ("Bochan") in view of Inukai et al. (*Jpn J Pharmacol* 1993; 61: 221-227) ("Inukai"), and further in view of Burt et al. (*Autoimmunity Rev* 1:133-38, May 2002) ("Burt"). The Examiner has also rejected claim 11 under 35 U.S.C. §103(a) as allegedly unpatentable over Bochan in view of Inukai and Burt, as applied to claims 1-8, 10, 12-16 above, further in view of Slavin et al. (U.S. Patent No. 6,428,782).

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Initially, Applicants note that both of the Examiner's §103(a) rejections rely on a combination of Bochan, Inukai and Burt. Applicants further note that the presently claimed invention is directed to methods for *preventing or otherwise reducing the risks* of development of diabetes. See independent claims 1 and 10. The claimed methods are achieved by exposing the immune system to a self-protein (proinsulin) antigen in such a manner to induce immune tolerance to that antigen.

Bochan discloses a method of reversing chemically induced diabetes in the rat by injection of HSCs infected with the adeno-associated virus containing the preproinsulin gene. That is, Bochan is directed to *reversing diabetes* using gene therapy. Bochan does ***not*** teach or suggest preventing or reducing the risks of development of diabetes by an antigen-specific immune tolerance-inducing strategy. Similarly, Burt does ***not*** teach or suggest preventing or

reducing the risks of development of diabetes.

The Examiner now relies upon the newly cited prior art, the Inukai (1993) reference, in an attempt to cure the deficiencies of Bochan and Burt. According to the Examiner, although Bochan does not teach preventing or reducing the risk of development of diabetes, Inukai supplements the deficiency by showing that the means for reversing the course of diabetes should also be capable of preventing and reducing the risk of developing diabetes. Inukai teaches using a novel reductase inhibitor TAT for allegedly treating diabetic neuropathy in rats, and reports the dosage as 8.8 mg/kg/day for prevention and 9.0 mg/kg/day for reversal (e.g. the abstract).

The Examiner also states that for any given treatment regimen, the underlying mechanism for reversing the course of diabetes generally should be the same for prevention. In fact, the Examiner alleges that it is harder to achieve course reversal for a disease than to prevent or reduce the risk of developing the disease. The Examiner has cited Inukai (1993) and Tian (*J. Immunol.* 179: 6762-6769, 2007) in support of her position in this regard.

Applicants respectfully submit that the Examiner's rejections are based on a misunderstanding of Inukai. Inukai is directed toward treating and reversing one diabetic complication: diabetic neuropathy caused by sorbitol accumulation in nerve cells in animals which have already developed diabetes. However, diabetic complications are wide-ranging and include: heart disease and stroke, neuropathies (nerve damage), diabetic retinopathy, erectile dysfunction, vascular complications, hypoglycemia and kidney disease.

Inukai discloses the use of an aldose reductase inhibitor, TAT, to treat diabetic neuropathy in diabetic rats. A TAT inhibitor is a small molecule compound which affects the polyol pathway and does not affect the level of glucose (See page 224, 2nd paragraph, last sentence of Inukai). The authors of the Inukai reference were studying the prevention and

reversal of sorbitol accumulation in the nerves of rats with diabetes, and *not* the prevention of diabetes.

The Examiner alleges that Inukai showed "that the means for reversing the course of diabetes should also be capable of preventing and reducing the risk of developing diabetes". Applicants respectfully submit that this is an incorrect statement. Inukai discloses that the treatment and reversal of diabetic complications were possible in STZ-treated rats, i.e., rats which already have diabetes. Thus, at best, Inukai showed treatment and reversal of the neuropathy complication caused by sorbitol accumulation which can be associated with diabetes. Inukai did ***not*** show or even suggest that this result means that the disclosed approach was able to prevent or reverse diabetes; i.e., prevent or reverse the autoimmune T-cell mediated destruction of pancreatic islet beta-cells. The complications disclosed in Inukai only occurred after the onset of diabetes in these rats. Hence, *the rats described by Inukai with decreased sorbitol accumulation were still diabetic.* All that Inukai achieved was the reversal or prevention of sorbitol accumulation. The disease of diabetes was not prevented, nor had the risk of developing diabetes been altered. There is no teaching or suggestion indicating that the polyol pathway inhibitor, TAT, would be of any use in preventing diabetes or reducing the risk of developing diabetes.

Accordingly, Inukai does not teach or suggest any means for preventing or reducing the risk of developing diabetes, and therefore does not cure the deficiencies of the combined teachings of Bochan and Burt.

Furthermore, the Tian reference was published in 2007, after the filing date of the instant application. Thus, the information disclosed therein cannot be relied upon by the skilled

artisan as providing either motivation or suggestion in attempting to arrive at the claimed invention.

Therefore, both of the Examiner's §103(a) rejections which rely on at least a combination of Bochan, Inukai and Burt, are overcome. Withdrawal of the rejections is respectfully requested.

In view of the foregoing, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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